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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,538	EGAN ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-21,23,25-27,29-37 and 39-52* is/are pending in the application.

4a) Of the above claim(s) *39-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-21,23,25-27 and 29-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-10,12-21,23,25-27,29-37 and 39-52* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

Applicant's amendment filed on 08 October 2003 is acknowledged and entered. Following the amendment, claim 38 is canceled, and claims 1, 12, 23, 27, 31-34 and 36 are amended.

Currently, claims 1-10, 12-21, 23, 25-27, 29-37 and 39-52 are pending, and claims 1-10, 12-21, 23, 25-27 and 29-37 are under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claim 38 are moot as the applicant has canceled the claim.

The new matter rejection of claims 2, 13, 25, and 29 made in the last Office Action is withdrawn in view of applicant's argument.

The prior art rejection of claim 31 under 35 U.S.C. 102(b) as being anticipated by Mashima et al. (Endocrinology, 1996, 137(9): 3969-76) is withdrawn in view of applicant's amendment.

Formal Matters:

The specification is objected to for the recitation of "$H^{7(1)}$, $G^{10(4)}$ ..." (line 29 on page 17, for example) as it is unclear what it is meant.

New Matter Rejection:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly amended claim 31 recites the limitation of "exclude hepatocyte growth factor". Although Applicants point out the support in the specification at page 15, lines 3-9, the Examiner cannot locate such a relevant support or basis, and therefore, the amendment constitutes new matter.

This is a new matter rejection.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 12-21, 23, 25-27 and 29-37 remain rejected under 35 U.S.C. 112; second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons set forth in the previous Office Actions, paper No. 10 and 15.

Applicants argument filed on 08 October 2003 has been fully considered, but is not deemed persuasive for reasons below.

At pages 13-14 of the response, the applicant argues that Webster's New College Dictionary defines "homologous" as "similar or corresponding in position, value, structure, or function" and "corresponding in structure and evolutionary origin"; that one of skill in the art would recognize that the claims recite growth factors having amino acid sequences that correspond in position, value, structure and function as the referents, GLP-1 and exendin-4, that therefore, it is not necessary to state an upper limit to the length of the claimed amino acid sequences. This argument is not persuasive because the term "substantially homologous" in the claims is a relative term, and when it is used to describe an amino acid sequence, it cannot clearly define the sequence structure of a polypeptide molecule. Additionally, "homologous" is not equal to "substantially homologous". Further, the term "substantially homologous" does not define an upper limit as to how many amino acids may be altered while remaining to be "substantially homologous to", and it is unclear what percent homology is considered substantial and at what point the homology becomes non-substantial. Thus, one of skill in the art would not be able to determine the metes and bounds of the claims.

Claim 31 is further indefinite because it is unclear what "$H^{7(1)}$, $G^{10(4)}$ ..." is meant.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12-21, 23, 25-27 and 29, 30-37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to an isolated population of insulin-producing cells made by contacting GLP-1 or exendin-4, does not reasonably provide enablement for claims to an isolated population of insulin-producing cells made by contacting growth factors having amino acid sequences *substantially homologous* to GLP-1 or exendin-4, or *fragment* thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims, for the reasons of record set forth in the last Office Action, paper No. 15, at pages 5-7.

Applicants argument, filed on 08 October 2003 has been fully considered, but is not deemed persuasive for reasons below.

At pages 14-16 of the response, the applicant argues that according to MPEP, with respect to the breath of a claim, the Examiner should determine what the subject matter is when the claim is considered as a whole, and the Examiner has failed examine the claims as a whole by focusing only on the clause "growth factors having amino acid sequences substantially homologous to ...". This argument is not persuasive because the instant enablement rejection is a scope rejection, i.e., the invention is not commensurate in scope with the claims. As such, the rejection is focused on the part that is not enabled rather than the part that is enabled. Additionally, the Examiner has considered the claims as a whole, and clearly defined the breath of the claims, the part that is enabled and the part that is not enabled in the very first paragraph of the rejection (see above).

At pages 16-18 of the response, the applicant argues that the Examiner incorrectly define the term "homologous" to mean only "having the same function, however, according to the dictionary, the phrase "amino acid sequences substantially homologous to" would describe

amino acid sequences "similar or corresponding in position, value, structure, ***or*** function" and "corresponding in structure and evolutionary origin" to a reference amino acid sequence, e.g., GLP-1 and/or exendi-4, and that one of skill in the art would recognize the recited growth factors having amino acid sequences substantially homologous to the structure and function of the referenced GLP-1 and Exendin-4, not just to function alone. Applicants further argue that the specification teaches that the claimed homologous growth factors can be made with additions, deletions or substitutions in the amino acid sequence of GLP-1 or exendin-4 without significantly changing their *structure* and activity. These arguments are not persuasive because the general definition of "homologous" from Webster's New College Dictionary is not known in the art for defining specific amino acid sequences. The term "homologous" is defined by relative terms in the dictionary, such as "similar or corresponding". As each amino acid sequence is comprised by specific amino acids in a precise order, terms such as "substantially homologous to" and "similar or corresponding" cannot be used to describe clearly an amino acid sequence. There is no way that one of skill in the art would recognize the exact sequence structure of such as growth factor that meets the limitation of being "substantially homologous to". [further, applicants own definition argument that the phrase "amino acid sequences substantially homologous to" would describe amino acid sequences "similar or corresponding in position, value, structure, ***OR*** function" still does not define the structure of the molecules as it is unclear what "amino acid sequences *similar in position*" means, i.e., any polypeptide with a particular residue at a particular position, for example? It is also unclear what "amino acid sequences *similar in value*" means, i.e., value of what? According to applicants definition, it seems that said polypeptide would not require anything else other than being "similar in position or value", which would encompass millions of polypeptides of similar size. As such, which of millions of the polypeptides would predictably induce insulin production? Additionally, according to the present specification, "amino acid sequences substantially homologous" to GLP-1 or exendin-4 means polypeptides that include one or more additions, deletions or substitutions in the amino acid sequence of GLP-1 or exendin-4 without appreciable loss of functional activity, which, given the broadest interpretation, reads on a functional equivalent that may not have sequence similarity as there is no upper limit as to how

many amino acids being changed, and it is unclear the metes and the bounds of the sequence identity that is considered "substantially homologous". Further, contrary to applicants argument in the response that the specification teaches that the claimed homologous growth factors can be made ... without significantly changing their *structure* and activity, the specification merely states "without appreciable loss of *functional* activity". Furthermore, the teachings on page 17 to 18 of the specification, as applicants pointed out, are merely exemplary, which fall within the scope of the claims, but do not define the metes and bounds of the claims. Therefore, for the reasons above, any functionally equivalent protein with no structure similarity to GLP-1 or exendin-4 would meet the limitation of the claims.

At pages 18-19 of the response, the applicant argues that unlike in Maizel, applicants teach proteins that are substantially homologous' to GLP-1 or exendin-4 whose respective structures are well known in the art, and thus the claimed growth factors are not defined only by their biological activity, and that the claims have been amended to specify five amino acid residues and the differentiating function. This argument is not persuasive because the amended limitation defining the five amino acid residues constitutes new matter as there is no support in the specification for such a claim limitation for the reasons above. Even if a molecule comprises the five defined amino acid residues, and has the recited functional activity, it still can be a functional equivalent as it may not have overall sequence homology to GLP-1 or exendin-4, as there really no structural limitation commensurate with the enablement in the claims. Applicants have merely provided a single polypeptide of GLP-1 or exendin-4, and have not pointed out domains or regions crucial to its required function. The claims encompass any polypeptide with the five amino acid in common, with no guidance regarding the selection of any other amino acids in the polypeptide nor their arrangement. Applicants have provided no evidence that these 5 amino acids, alone or any combination, would predictably result in a polypeptide with the required function. It has been shown in the prior art that any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter or even abolish its functional properties. For instance, Shepard et al. (Nature, 1981, 294:563-565) teach that a single amino acid change at the position 141 of human IFN-β abolishes its antiviral activity (the abstract and Table 1). Therefore, one of skilled in the art

would not be able to make a polypeptide with the desired functional property merely based on five defined amino acids without any correlation to the function of the polypeptide. Further, as addressed above, the claims, given the broadest interpretation, encompass functional equivalents of GLP-1 or exendin-4, and one of skill in the art would not know how to make all species of "a growth factor" in a manner commensurate in scope with the claims without undue experimentation.

Note: the newly cited reference is merely used to rebut applicants arguments, and it is not for sustaining any new ground of rejection.

Claims 1, 12, 23, 27, 31-34, and 36 remain further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the last Office Action, paper No. 15, at pages 7-8.

Applicants argument, filed on 08 October 2003 has been fully considered, but is not deemed persuasive for reasons below.

At page 20 of the response, the applicant argues that the level of skill and knowledge in the art is high; that applicants provide detailed, known referent structures of GLP-1 and exendin-4, and "substantially homologous" is meant an sequence including conservative amino acid substitutions or high sequence identity; that the function of these growth factor is the differentiation of non-insulin-producing cells into insulin-producing cells, and thus, the specification has described the structure and common function, and applicants were in possession of the claim growth factors. This argument is not persuasive because, although the specification provides a correlation between the full length structure and function, it does not detail any substructures from the full length that retain the function. The inclusion of 5 amino acid residues does not provide adequate structure since these 5 amino acids have not been correlated with the desired function of the polypeptides. Additionally, as the claims encompass the functional equivalents of GLP-1 or exendin-4, and the specification does not disclose any of such growth factors meeting the limitations of the claims, one of skill in the art would have no

basis to derive the claimed ranges of "growth factors" from the instant disclosure, and thus, would not be able to envision the detailed chemical structure of the encompassed, and to make such growth factors even though the level of skill and knowledge in the art is high. Further, the claims recite that the growth factors having amino acid sequences substantially homologous to, not the growth factors *and* fragments thereof.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 26, 27, 30, 31 and 35-37 remain rejected under 35 U.S.C. 102(b) as being anticipated by Eng, US 5,424,286, for the reasons set forth in the previous Office Actions, paper No. 10 and 15.

Applicants argument filed on 08 October 2003 has been fully considered, but is not deemed persuasive for reasons below.

At pages 21-23 of the response, the applicant made the similar argument as that in the last response, namely that according to MPEP and case laws, the Examiner has the burden to show that a missing element of a claim is inherently present in the prior art and this missing descriptive matter would be recognized by person of the skill in the art, that inherency may not be established by probabilities or possibilities, and that the prior art does not teach the contact of the growth factor with non-insulin producing cells for at least 24 hours, nor the differentiation of the cells into insulin producing cells by such contact, and thus it does not inherently anticipate the claimed invention. Applicant further argue that in *In re Zierden*, 162 USPQ 102 (CCPA 1969), the court held that because the prior art did not inherently teach that the industrial waters contained alluvium, the disclosed method did not necessarily result in the removal of alluvium. These arguments are not persuasive and *In re Zierden* does not apply in the instant situation for the reasons addressed in the last office action, and below.

The method in *In re Zierden* is related to a method of removing alluvium from industrial waters. As different industrial waters may contain different ingredients, a method of removing one element from one type of industrial waters may not necessarily be useful for another type of industrial waters because the elements being removed may not be the same among different types of industrial waters, and different chemical elements may not be removed by the same method. In contrast, in the present situation, the biologic subjects or the cells being treated have the same anatomic structures and biochemical components, which are not questionable probabilities or possibilities even though the prior art does not mention such, therefore, as the active ingredient and the method steps used are the same between the prior art and the present invention, the results or the consequences would be inherently the same. It is unclear how and why they should or could be different otherwise, even though the prior art does not explicitly mention the contact for at least 24 hours, and the result of differentiation of the cells.

At page 24 of the response, the applicant repeatedly argues that the Office is incorrect when it alleges that methods of stimulating insulin release in a mammal as taught in the prior art patent are the same as the claimed methods, and that the methods of the prior art necessarily differentiate non-insulin-producing cells into insulin-producing cells by contacting for at least 24 hours. This argument is not persuasive because the Examiner merely states that the method *steps* are the same between the prior art reference and the present invention. As such, even though the prior art does not explicitly teaches the differentiation of non-insulin-producing cells into insulin-producing cells, it would be an inherent property when the active ingredients and the method steps are the same. As stated in *In re Best, Bolton, and Shaw* ((CCPA) 195 USPQ 430), [i]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.

At pages 24-26 of the response, the applicant argues that the Examiner ignores the presence of degradative enzymes in the subject, that the present specification states that a cell can be contacted by a growth factor by ... bolus delivery, ..., GLP-1 has a short half-life of several minutes, ... a bolus of GLP-1 would have contact with the cell for minutes, and a bolus of exendin-4 would contact with the cell for hours, that a physiologically effective level of GLP-1 needs continuously maintained, and that the prior art patent teaches giving GLP-1 only over a short period of time, and thus, the Office has failed to meet its burden of showing that the missing matter in the prior art reference. Applicants further argue that the prior art reference teaches an insulinotropic effect on the beta cells of a subject, and there is no suggestion of contact of non-insulin producing cells for 24 hours. These arguments are not persuasive because, while the Examiner acknowledges the presence of degradative enzymes in the subject, and does not apply the rejection to claims directed to in vitro method, such argument must apply both ways. Although the claims recite "contacting for at least 24 hours", there is no claim limitation indicating that "contacting for at least 24 hours" is the result of specific method steps different from the administering steps of the prior art, such as by continuous infusion for 24 hours, for example. Given the fact that the present specification teaches, as pointed by applicants, that "a cell can be contacted by a growth factor by ... bolus delivery", and that the prior art teaches bolus doses of GLP-1 or exendin-4 administered to the animals, if "contacting" in the present invention can last for at least 24 hours, so would the method taught by the prior art in the absence of evidence to the contrary, which would indicate, for example, the bolus deliveries between the prior art and the instant invention are different.

With respect to the insulinotropic effect of the growth factors on the beta cells in a subject, not non-insulin producing cells taught by the prior art reference, the effect of the growth factors on non-insulin producing cells would be inherent property for the reasons above, as one cannot prevent such effect from happening within the same subject.

Claims 23, 26, and 31 remain rejected under 35 U.S.C. 102(b) as being anticipated by Dupre (WO 95/31214, provided by applicants), for the reasons set forth in the previous Office Actions, paper No. 10 and 15.

Applicants argument filed on 08 October 2003, at pages 26-19 has been fully considered, but is not deemed persuasive for reasons above as the most of the arguments are based on the same ground as that for the rejection above ("contacting for at least 24 hours", and the inherency), and for the reasons below.

Besides the repeated argument as that for above rejection, applicants argue at page 27 of the response that in WO 95/31214, the growth factor was *administered* to subject for no greater than 2 hours, and therefore, it cannot anticipate the present claims. This argument is not persuasive because, as addressed above, there is no limitation in the present claims indicating that it is the specific *administering* step differing from that of the prior art and ensuring the contacting for 24 hours. As such, if "contacting" in the present invention can last for at least 24 hours, so would the method taught by the prior art in the absence of evidence to the contrary.

At page 28 of the response, the applicant argues that WO 95/31214 teaches that GLP-1 can be used to treat type I diabetic patients who have some endogenous insulin secretion, and does not teach the use of GLP-1 for treating diabetic patients who no longer have endogenous insulin secretion. This argument is not persuasive because the prior art reference teaches a method of treating type I diabetes with a GLP-1 analog, and exemplifies the treatment of type I diabetic patients who have some endogenous insulin secretion. However, the prior art reference never excludes any subtype of type I diabetic patients from such a treatment, for example, type I diabetic patients who no longer have endogenous insulin secretion. As such, the reference remains anticipating the present claims.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Dong Jiang, Ph.D.
Patent Examiner
AU1646
12/23/03

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